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Bromoamides as Starting Materials in the Synthesis of α-Hydroxy- and α-Alkoxy Derivatives

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BROMOAMIDES AS STARTING MATERIALS IN THE SYNTHESIS OF α-HYDROXY- AND α-ALKOXY DERIVATIVES

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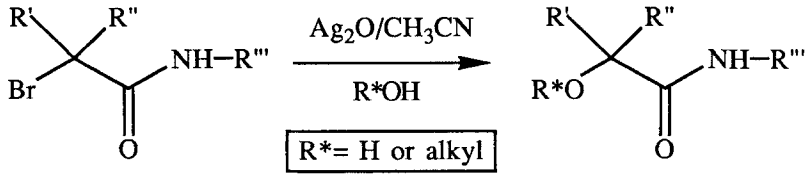
Abstract: Silver oxide promotes substitution of the bromine at position 2 of α-bromocarboxamides, with a hydroxyl or an alkoxyl group.

α-Hydroxy- and α-alkoxyderivatives of amides are important compounds as intermediates in organic synthesis and/or as biologically active derivatives in pharmaceutical chemistry.

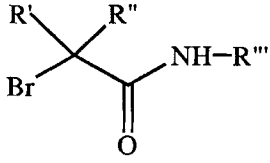
While a variety of methods are disposable for the production of α-hydroxy carbonyl compounds [1], literature is not so rich in studies on the α-hydroxylation neither of carboxylic acids [2,3,4,5], nor of esters [6,7,8] and amides. α-Hydroxylation of amides is moreover limited to N,N-dialkyl ones [9,3] except few particular cases.

We wish to report here our method that proceeds via substitution of the bromine at the alfa carbon of the pertinent α-bromocarboxamide by both the hydroxyl and the alkoxyl groups: the formation of the ether linkage is achieved using silver oxide as condensing agent.



α-Hydroxyderivatives of α-bromoisobutyramides, as prototype of starting materials hindered at C alfa, (Scheme 1) are obtained as pure products, in good yields, stirring reactions at room temperature from 90 min to 12 hours.

Scheme 1

bromoamide	R' = R" = CH_3	hydroxy derivative
	R''' = CH_2-C_6H_5	90% ; 12 h
	R''' = C_6H_5	89% ;1.5 h
	R''' = $C(CH_3)_3$	86% ;1.5 h
	R''' = CH_3	75% ; 3 h

A preliminary study on hydroxylation of α-bromopropionamides (e.g. N-benzyl- and N-terbutilamides) seems to evidence the same trend, but reaction time is longer while yields are good.

To shed light on further possibilities of the method, we synthesized some α-alkoxyderivatives of α-bromo-N-benzyl-isobutyramide (Scheme 2) and we found that two side products were present, determined as the pertinent hydroxy and elimination derivatives. While strictly anhydrous conditions can avoid hydroxyderivative formation, dehydrobromination product is always present whose amount depending on steric hindrance and nucleophilicity of the substituting alcohol and nature of NH moiety. Preliminary investigations showed that this side product indeed seems not present in other alkoxyamides derivatives, i.e. cycloalkanamides or propionamides.

This method cannot be useful when aprotic amides are employed [10].

Scheme 2

Pattern of reaction of α-bromo-N-benzyl-isobutyrlamide with various alcohols in the presence of Ag_2O

partner	alkoxy derivative	hydroxy derivative	elimination derivative
C_2H_5-OH	70% ; 66 h	10%	10%
$(CH_3)_3$-C-OH	56% ; 3 days	12%	12%
C_6H_5-OH	50% ; 3 days	13%	13%

Reaction times become longer and yields lower as the steric hindrance of nucleophil increases. In the case of 2-adamanthol no reaction products were observed also refluxing 5 hours.

We can therefore conclude that (1) hydroxylation yields of all the tested bromoamides were satisfactory; (2) in the case of alkoxylations (a) the reaction yields depend upon the steric hindrance of the alcohol and (b) presence and amount of side products depend upon the primary, secondary or tertiary nature of C alfa carbon and the nature of NH moiety.

Typical procedure:

2-bromo-N-benzyl-isobutyramide (512 mg, 2 mmol) dissolved in moist CH_3CN (5 ml) in the presence of silver oxide (232 mg, 1 mmol) was stirred overnight at room temperature. The reaction mixture was purified by passing the solution on a column filled by neutral alumina covered with a layer of Celite 577. Evaporation to dryness gave an oil (350 mg, 90.5%, Rf.0.25 in ethyl acetate-toluene 1:4) that cristallyzed by treatment with ethyl ether (colorless solid, pf.133-35°C). ^{1}H-NMR ($CDCl_3$): δ 1.40 (s, 6H, $2CH_3$); 4.35 (d, 2H, CH_2, J=5.22Hz); 7.35 (s, 5H, C_6H_5). Elem. anal., found % (calcd. for $C_{11}H_{15}NO_2$): C, 68.42 (68.37); H, 7.88 (7.82); N, 7.35 (7.24).

If α-alkoxyderivatives are prepared, distilled CH_3CN must be used beside the proper alcohols.

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